

US009914773B2

# (12) United States Patent

Low et al.

# (10) Patent No.: US 9,914,773 B2

(45) **Date of Patent:** Mar. 13, 2018

# (54) ANTI-HUMAN FOLATE RECEPTOR BETA ANTIBODIES AND METHODS OF USE

(71) Applicants: Purdue Research Foundation, West
Lafayette, IN (US); The United States
of America, as Represented by the
Secretary Department of Health and
Human Services, Washington, DC (US)

(72) Inventors: Philip S. Low, West Lafayette, IN (US); Dimiter S. Dimitrov, Frederick, MD (US); Yang Feng, Frederick, MD (US); Jiayin Shen, San Diego, CA (US)

(73) Assignees: PURDUE RESEARCH
FOUNDATION, West Lafayette, IN
(US); THE UNITED STATES OF
AMERICA DEPEARTMENT OF
HEALTH AND HUMAN SERVICES,
Washington, DC (US)

(\*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 29 days.

(21) Appl. No.: 14/524,304

(22) Filed: Oct. 27, 2014

# (65) Prior Publication Data

US 2015/0110798 A1 Apr. 23, 2015

### Related U.S. Application Data

- (63) Continuation of application No. 13/790,881, filed on Mar. 8, 2013, now Pat. No. 8,871,206, which is a continuation-in-part of application No. PCT/US2011/050943, filed on Sep. 9, 2011.
- (60) Provisional application No. 61/381,340, filed on Sep. 9, 2010.

(51)	Int. Cl.	
	C07K 16/28	(2006.01)
	C07K 14/705	(2006.01)
	A61K 38/00	(2006.01)
	A61K 9/00	(2006.01)
	A61K 9/127	(2006.01)
	A61K 47/48	(2006.01)
	A61K 49/00	(2006.01)
	A61K 49/16	(2006.01)
	A61K 51/10	(2006.01)

(52) U.S. Cl.

# (58) Field of Classification Search

None

See application file for complete search history.

#### (56) References Cited

#### U.S. PATENT DOCUMENTS

4,522,811	A 6/1985	Eppstein et al.
5,798,230	A 8/1998	Bornkamm et al.
6,001,329		Buchsbaum et al.
2003/0232333 A	A1 12/2003	Ladner et al.
2008/0260812	A1 10/2008	Matsuyama et al.
2010/0055034	A1 3/2010	Martin et al.

# OTHER PUBLICATIONS

Vajdos et al. (J Mol Biol. Jul. 5, 2002;320(2):415-28 at 416).\* Brown et al. (J Immunol. May 1996;156(9):3285-91).\*

Antohe et al, "Increased uptake of folate conjugates by activated macrophages in experimental hyperlipemia," *Cell Tissue Res.*, 320:277-285, Feb. 16, 2005.

Antony, "The biological chemistry of folate receptors," *Blood*, 79(11):2807-2820, Jun. 1, 1992.

Ayala-Lopez et al., "Imaging of atherosclerosis in apoliprotein e knockout mice: targeting of a folate-conjugated radiopharmaceutical to activated macrophages," *J Nuc Med*, 51(5):768-774 Epub Apr. 15, 2010

Bender et al., "Recombinant human antibodies: linkage of an Fab fragment from a combinatorial library to an Fc fragment for expression in mammalian cell culture," *Hum Antibodies Hybridomas*, 4(2):74-79, Apr. 1993.

Blaser et al., "Induction of folate receptor type beta in a bone marrow engraftment model of acute myelogenous leukemia," *Leukemia*, 21:2233-2235, Epub Jun. 7, 2007.

Boerner et al., "Production of antigen-specific human monoclonal antibodies from in vitro-primed human splenocytes," *J. Immunol.*, 147(1): 86-95, Jul. 1, 1991.

Brown et al., "P38 MAP kinase inhibitors as potential therapeutics for the treatment of joint degeneration and pain associated with osteoarthritis," *J. Inflamm. (Lond.)*, 5:22, Dec. 4, 2008.

Chaudhary et al., "A proper amino terminus of diphtheria toxin is important for cytotoxicity," *Biochem Biophys Res Commun.*, 180(2):545-551, Oct. 31, 1991.

Chen et al, "Detection of dysplastic intestinal adenomas using a fluorescent folate imaging probe," *Mol Imaging*. 4(1):67-74, Jan.-Mar. 2005.

Chen et al., "Arthritis imaging using a near-infrared fluorescence folate-targeted probe," *Arthritis Res Ther.*, 7(2):R310-317, Epub Jan. 14, 2005.

Elnakat and Ratnam, "Distribution, functionality and gene regulation of folate receptor isoforms: implications in targeted therapy," *Adv Drug Deliv Rev* 56(8):1067-1084, Apr. 29, 2004.

Eshhar, "The T-Body Approach: Redirecting T Cells with Antibody Specificity," *Therapeutic Antibodies (Handbook of Experimental Pharmacology)*: 181, Chernajovsky and Nissim (eds.), pp. 329-342, Dec. 13, 2007.

#### (Continued)

Primary Examiner — Brian Gangle
Assistant Examiner — Andrea K McCollum
(74) Attorney, Agent, or Firm — Wenderoth, Lind &
Ponack, L.L.P.

# (57) ABSTRACT

Human anti-human folate receptor beta antibodies and antigen-binding fragments thereof are described, as well as methods of using such antibodies and fragments to treat inflammatory disorders or cancers expressing cell surface  $FR\beta$ .

# 17 Claims, 12 Drawing Sheets